Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Olfactory dysfunction incidence and resolution amongst 608 patients with COVID-19 infection

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ABSTRACT

Purpose: Olfactory dysfunction (OD) is a common presenting sign of coronavirus-19 (COVID-19) infection and remains persistent in up to 7 % of patients one year after diagnosis. However, demographic, socioeconomic, and medical risk factors for persistent OD are not well understood. This study aims to determine risk factors for development and persistence of OD amongst patients with COVID-19 infection.

Materials and methods: This prospective, observational questionnaire study was performed at a tertiary-level, academic center. Patients with history of a positive COVID-19 diagnosis were sent an online questionnaire. Patients' self-reported survey responses for OD and resolution were assessed for associations with demographic variables, socioeconomic factors, and clinical data.

Results: In total, 608 of 26,094 patients (77.6 % women, mean age 42.7 ± 17.4 years, range 9 months-92 years) completed the survey. OD was reported by 220 (36.2 %) patients, and 139 (63.2 %) patients achieved resolution. Patients with OD were more likely to have other sinonasal and flu-like symptoms, and had a hospitalization rate of 2.7 %. There were no significant differences in age, gender, occupational or residential factors, or medical comorbidities incidence of OD development. Women reported higher rates of persistent OD (88.9 % vs 77.0 %, $p = 0.045$). The OD recovery rates amongst active and resolved COVID-19 infections was 27.0 % and 70.0 %, respectively ($p < 0.001$).

Conclusions: There was a low hospitalization rate amongst patients reporting OD. One-third of patients with COVID-19 self-reported OD, and two-thirds of patients achieve OD resolution. Survey respondents with active COVID-19 infection and female gender were more likely to report persistent OD.

1. Introduction

Olfactory dysfunction (OD) has been established as a common presenting symptom in COVID-19 patients. Viral tropism for cells constituting the olfactory epithelium can lead to colonization, inflammation, and damage in the nasal cavity. OD can occur in the absence of other symptoms and has been reported as an early sign of COVID-19 infection [1,2]. Notably, younger and healthier patients have presented more commonly with isolated OD [3].

As the cumulative number of patients with COVID-19 infection surpasses 600 million worldwide, there are an increasing number of patients reporting persistent symptoms, also known as "long COVID" or post-acute COVID syndrome (PACS) [4,5]. OD is the most commonly reported persistent symptom in patients with PACS [6]. Up to 7 % of patients remain anosmic for 12 months or longer after the onset of infection [7,8].

The American Academy of Otolaryngology-Head and Neck Surgery released a COVID-19 anosmia reporting tool for physicians to screen patients, which includes patient age, gender, time of diagnosis, infection source, concurrent comorbidities, and whether the anosmia occurred before or after diagnosis [9,10]. Initial reports based on this reporting tool have demonstrated that only 27 % of patients report anosmia improvement one week after COVID-19 diagnosis. As anosmia can severely impact quality of life, there is a need to further our understanding of risk factors for both anosmia development and long-term anosmia resolution [11].

This study aimed to determine the incidence of smell and taste

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Abbreviations

BMI	body mass index
CI	confidence interval
COVID-19	coronavirus-2019
HR	hazards ratio
IQR	interquartile range
OD	olfactory dysfunction
OR	odds ratio
SD	standard deviation

Table 1
Descriptive characteristics of all survey respondents ($n = 608$).

Variable	n = 608
Mean age at survey response, in years	42.71 ± 17.36
Gender (%)	
Female	472 (77.6)
Male	136 (22.4)
Identifiable source of COVID-19 infection	364 (59.9)
Risk factors	
Healthcare worker (%)	315 (51.8)
First responder (%)	10 (1.6)
Close contact with a confirmed case (%)	190 (31.2)
Homeless (%)	4 (0.7)
Congregant living (%)	12 (2.0)
High risk travel (%)	22 (3.6)
Occupational exposures (%)	8 (1.3)
Other risk factors (%)	61 (10.0)
No risk factors (%)	150 (24.7)
Medical comorbidities	211 (47.6)
Smoking (%)	34 (5.6)
Head trauma (%)	7 (1.2)
Cancer or immunocompromised (%)	13 (2.1)
Sinusitis or allergies (%)	180 (29.6)
Nasal polyps (%)	7 (1.2)
Chronic Kidney Disease (%)	6 (1.0)
Transplant on immunosuppressants (%)	1 (0.2)
Taking steroids or immunomodulators (%)	15 (2.5)
Liver disease (%)	5 (0.8)
Morbid obesity (BMI > 40) (%)	68 (11.2)
Chronic respiratory disease/Asthma (%)	82 (13.5)
Cardiac disease (%)	25 (4.1)
Neurologic disease (%)	8 (1.3)
Symptoms	
Both anosmia and dysgeusia	191 (31.4)
Anosmia only	20 (4.7)
Dysgeusia only	34 (5.6)
Neither anosmia nor dysgeusia	354 (58.2)
Current COVID-19 infection status	
Active	106 (17.4)
Recovered	502 (82.6)

dysfunction amongst patients with COVID-19. We aimed to determine associations between clinical, demographic, socioeconomic, and occupational factors that may put patients at increased risk for developing disordered taste and smell. These findings of this study aim to provide more accurate counseling for patients regarding expectations of OD resolution.

2. Materials and methods

This prospective, observational questionnaire study received University Hospitals Cleveland Medical Center Institutional Review Board approval (IRB# 202004471). Patients who received a laboratory-confirmed positive COVID-19 diagnosis via polymerase chain reaction (PCR) test between August 2021 and November 2022 at a tertiary-care academic center were included in the recruitment cohort. Patients were excluded if there was no email address listed in the electronic medical records or if the patient was deceased.

Table 2
Descriptive characteristics of patients who had anosmia versus no anosmia.

Variable	Anosmia ($n = 220$)	No anosmia ($n = 388$)	P value
Age (median [IQR])	40.00 [31.00, 55.00]	41.50 [30.00, 55.25]	0.787
Gender (%)			0.106
Female	179 (81.4)	293 (75.5)	
Male	41 (18.6)	95 (24.5)	
Identifiable source of COVID-19 infection	83 (37.7)	161 (41.5)	0.390
Risk factors			
Healthcare worker (%)	107 (48.6)	208 (53.6)	0.272
First responder (%)	4 (1.8)	6 (1.5)	0.753
Close contact with a confirmed case (%)	64 (29.1)	126 (32.5)	0.413
Homeless (%)	1 (0.5)	3 (0.8)	1
Congregant living (%)	4 (1.8)	8 (2.1)	1
High risk travel (%)	8 (3.6)	14 (3.6)	1
Occupational exposures (%)	4 (1.8)	4 (1.0)	0.469
No risk factors (%)	61 (27.7)	89 (22.9)	0.204
Medical comorbidities			
Smoking (%)	15 (6.8)	19 (4.9)	0.360
Head trauma (%)	3 (1.4)	4 (1.0)	0.708
Cancer (%)	4 (1.8)	9 (2.3)	0.778
Sinusitis or allergies (%)	64 (29.1)	116 (29.9)	0.854
Nasal polyps (%)	3 (1.4)	4 (1.0)	0.708
Chronic Kidney Disease (%)	3 (1.4)	3 (0.8)	0.673
Prior organ transplant (%)	1 (0.5)	0 (0.0)	0.362
Taking steroids or immunomodulators (%)	5 (2.3)	10 (2.6)	1
Liver disease (%)	0 (0.0)	5 (1.3)	0.165
Morbid obesity (BMI > 40) (%)	30 (13.6)	38 (9.8)	0.180
Chronic respiratory disease/ Asthma (%)	24 (10.9)	58 (14.9)	0.176
Cardiac disease (%)	6 (2.7)	19 (4.9)	0.287
Neurologic disease (%)	4 (1.8)	4 (1.0)	0.469
No comorbidities (%)	62 (42.8)	149 (50.0)	0.157
Associated symptoms			
Fever (%)	93 (42.3)	15 (3.9)	<0.001
Chills (%)	109 (49.5)	15 (3.9)	<0.001
Malaise (%)	107 (48.6)	13 (3.4)	<0.001
Cough (%)	147 (66.8)	18 (4.6)	<0.001
Headache (%)	143 (65.0)	21 (5.4)	<0.001
Nasal congestion (%)	155 (70.5)	14 (3.6)	<0.001
Rhinorrhea (%)	97 (44.1)	12 (3.1)	<0.001
Diarrhea (%)	46 (20.9)	4 (1.0)	<0.001
Nausea/Vomiting (%)	46 (20.9)	6 (1.5)	<0.001

Each week, 1500 patients who met inclusion criteria were sent a recruitment email. Patients were prioritized by recency of COVID test. The email included a description of the study and a hyperlink to a REDCap survey. Survey links were emailed to patients between March 2022 and October 2022. Patients were able to decline to participate or give informed consent to participate electronically. Pediatric patients who were identified as potential survey subjects were contacted through their parents for participation in the study. Patients were contacted by email one time to inform of participation in the study. No deadlines for survey response were mandated.

2.1. Survey instrument

The REDCap survey included questions about status of smell loss and recovery outcomes (Supplemental Fig. 1). Recruitment began March 29, 2022 and data collection ceased on November 21, 2022. The primary outcome was incidence of OD. Secondary outcomes were resolution of OD and presence of concurrent symptoms. OD presence and resolution were determined in a binary manner (yes or no) based on patients' self-reported survey response.

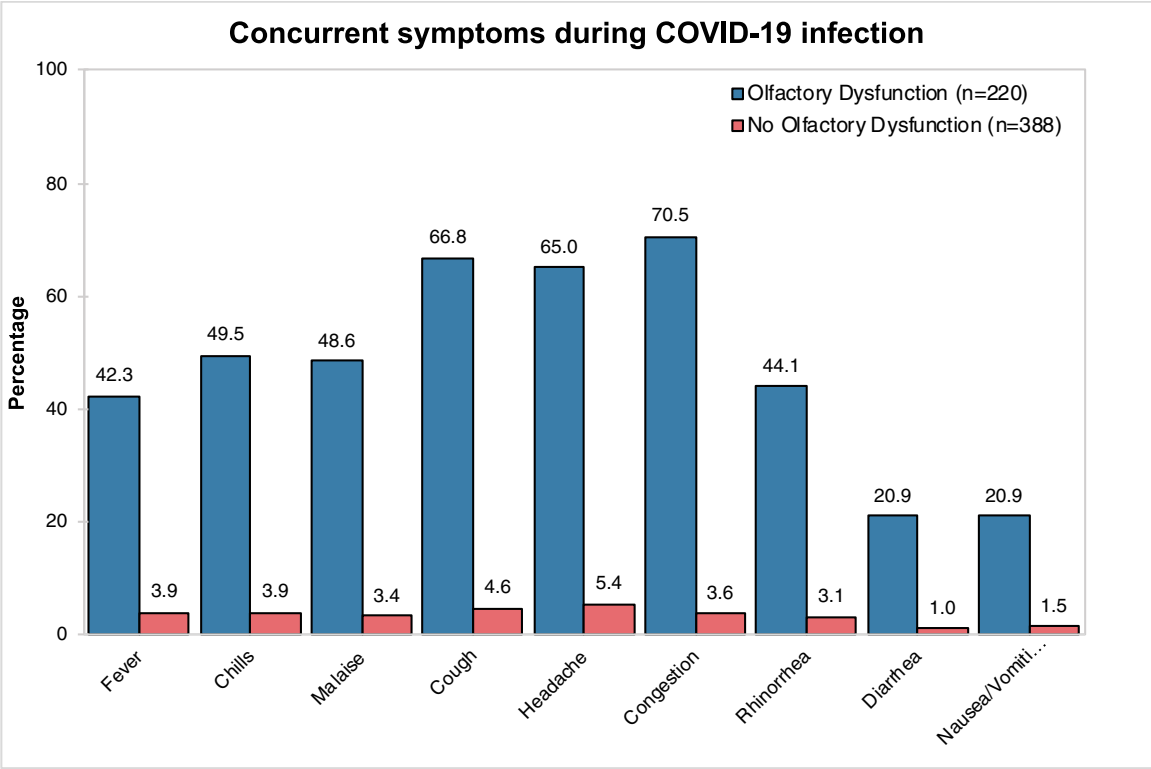

Fig. 1. Concurrent symptoms during COVID-19 infection.

2.2. Data collection

Demographic and clinical information for each patient were collected and managed using the REDCap electronic data capture tool [12]. Variables of interest included age, gender, location at time of diagnosis (inpatient or outpatient), source of COVID-19 infection, risk factors, comorbidities, concurrent symptoms, current infectious status, resolution of anosmia, and whether medical treatment was provided during the COVID-19 clinical course.

2.3. Statistical analysis

Categorical factors were described with frequencies and percentages, and compared using Pearson's Chi-square tests or Fisher's exact test. Normal variables were summarized with means and standard deviation (SD) and non-normal variables were summarized with medians and interquartile range (IQR). Continuous variables were compared using Student's *t*-test or Kruskal-Wallis test. All statistical analyses were performed in R software (version 3.5, Boston, MA) with p-values < 0.05 considered significant.

3. Results

3.1. Study population

In total, 608 patients completed the survey, with a response rate of 2.3 % (Table 1). The study cohort was comprised of 77.6 % women, and mean age was 42.7 ± 17.4 years (range, 9 months to 92 years) at time of survey response. Median time between positive COVID-19 test and survey response was 36 days (interquartile range, 8 to 199 days; range, 3 to 547 days). An identifiable source of COVID-19 infection was reported by 364 (59.9 %) patients. The most common risk factor reported was occupation as a healthcare worker, which 51.8 % of the survey respondents noted. The second most common risk factor was close contact with a confirmed COVID-19 positive case, which was reported by 190 (31.2 %) patients. Medical comorbidities were reported by 211 (47.6 %) of the survey respondents, the most common of which were sinusitis or allergies (29.6 %), chronic respiratory disease or asthma (13.5 %), morbid obesity (11.2 %), and smoking (5.6 %). Table 1 lists other less common risk factors and medical comorbidities.

3.2. Symptoms

OD was reported by 220 (36.2 %) patients. OD was first noticed before COVID-19 diagnosis in 69 (31.4 %) patients, whereas OD was noticed after COVID-19 diagnosis in 151 (68.6 %) patients. Dysgeusia was reported by 225 (37.0 %) patients. There were 191 (31.4 %) patients who reported having both OD and dysgeusia, 29 (4.7 %) who reported OD only, 34 (5.6 %) who reported dysgeusia only, and 354 (58.2 %) who reported neither OD nor dysgeusia. There were no significant differences in age, gender, occupational or residential factors, or medical comorbidities when comparing OD versus no OD cohorts (Table 2). The incidence of concurrent upper respiratory and flu-like symptoms was significantly higher in the OD cohort, and these included fever, chills, malaise, cough, headache, nasal congestion, rhinorrhea, diarrhea, and nausea/vomiting (all $p < 0.001$) (Fig. 1). Of patients reporting OD, 6 (2.7 %) patients required hospitalization for their COVID-19 infection.

3.3. Resolution of anosmia

Of 220 patients who reported OD, 37 (16.8 %) still had active COVID-19 infection at time of survey response, and 183 (83.2 %) had recovered from symptoms of COVID-19. The OD recovery rates amongst active and recovered COVID-19 symptoms was 27.0 % and 70.0 %, respectively ($p < 0.001$). Overall, OD resolution was reported by 139 (63.2 %) patients. Age, smoking history, occupational risks, residential risks, and medical comorbidities were not significantly different between those who achieved resolution and those with persistent OD (Table 3). Female gender was associated with a higher rate of persistent OD (88.9 % vs 77.0 %, $p = 0.045$). Current active COVID-19 symptoms

Table 3
Characteristics of patients who had resolution versus no resolution of olfactory dysfunction.

Variable	Olfactory dysfunction resolved ($n = 139$)	Olfactory dysfunction did not resolve ($n = 81$)	P value
Mean age (SD)	42.71 (16.13)	43.84 (15.56)	0.611
Gender (%)			0.045
Female	107 (77.0)	72 (88.9)	
Male	32 (23.0)	9 (11.1)	
Identifiable source of COVID-19 infection	87 (62.6)	50 (61.7)	1
Risk factors			
Healthcare worker (%)	66 (47.5)	41 (50.6)	0.757
First responder (%)	4 (2.9)	0 (0.0)	0.309
Close contact with a confirmed case (%)	39 (28.1)	25 (30.9)	0.773
Homeless (%)	1 (0.7)	0 (0.0)	1
Congregant living (%)	4 (2.9)	0 (0.0)	0.309
High risk travel (%)	2 (1.4)	6 (7.4)	0.056
Occupational exposures (%)	3 (2.2)	1 (1.2)	1
Medical comorbidities			
Smoking (%)	13 (9.4)	2 (2.5)	0.094
Head trauma (%)	2 (1.4)	1 (1.2)	1
Cancer (%)	2 (1.4)	2 (2.5)	0.977
Sinusitis or allergies (%)	39 (28.1)	25 (30.9)	0.773
Nasal polyps (%)	2 (1.4)	1 (1.2)	1
Chronic Kidney Disease (%)	3 (2.2)	0 (0.0)	0.466
Prior organ transplant (%)	1 (0.7)	0 (0.0)	1
Taking steroids or immunomodulators (%)	3 (2.2)	2 (2.5)	1
Morbid obesity (BMI > 40) (%)	17 (12.2)	13 (16.0)	0.554
Chronic respiratory disease/asthma (%)	14 (15.4)	7 (13.0)	0.876
Cardiac disease (%)	4 (2.9)	2 (2.5)	1
Neurologic disease (%)	2 (1.4)	2 (2.5)	0.977
Current COVID 19 infection status (%)			<0.001
Active	10 (7.2)	27 (33.3)	
Recovered	129 (92.8)	54 (66.7)	

were more commonly reported in the persistent OD cohort (33.3 % vs. 7.2 %, $p < 0.001$) (Fig. 2).

4. Discussion

This survey-based study assessed olfactory dysfunction in a large cohort of patients with COVID-19 infection. OD was reported by one-third of patients with COVID-19 infection, and was highly co-occurring with dysgeusia and flu-like symptoms. There was a low hospitalization rate amongst patients reporting OD (2.7 %). The resolution rate was 63 % overall, and increased to 70 % amongst those who had recovery from COVID-19 symptoms.

Our cohort had a self-reported OD incidence of 36 %. This rate is higher than several prior studies evaluating PACS (19–32 %) and lower than other studies (47–98 %) [24,27–36]. Differences in anosmia prevalence may reflect shifts in the SARS-CoV-2 strain over time, as well as geographic differences in patient populations. Differences in prevalence may also reflect study methodology, as self-reported rates are likely lower than studies with objective olfactory testing [34].

In our cohort, female respondents were more likely to report persistent anosmia, despite similar gender prevalence between those with active and recovered COVID-19 symptoms. This finding supports several prior studies. Amongst non-hospitalized patients, Subramanian et al. showed that anosmia was the most common persistent symptom of long COVID [6]. Further, risk factors for long COVID were female sex, lower socioeconomic status, current or former smoking status, and obesity. Female sex has been identified as a risk factor for long COVID in several prior studies [13–17]. Sehanobish et al. also showed that male gender was associated with lower rates of ageusia (OR 0.56, 95 % CI 0.38–0.82) [18]. Sehanobish has also shown that male gender is associated with an earlier recovery in taste (HR 1.44, 95 % CI 1.05–1.98) [18]. There may be several explanations for the sex differences seen in COVID-19 disease course. Female patients have higher serum SARS-CoV-2 IgG antibody levels, which may be protective against severe COVID-19 in the short course but with unknown long-term effects [19]. Downstream gene targets of the androgen receptor include transmembrane protease serine 2 (TMPRSS2), which can variably affect SARS-CoV-2 spike protein binding and entry [20]. Furthermore, hormonal differences can affect immune response; namely, endogenous estrogens have been shown to reduce hyperinflammatory responses to influenza infections in mice [21,22]. Gender differences in rates of survey completion may also contribute to findings.

Only 2.7 % of patients with OD required hospitalization for their COVID-19 infection, suggesting its association with a milder disease course. In contrast, the hospitalization rate is higher (8.4 %) amongst allcomers of COVID-19 [23]. Vaira et al. argues that anosmia is underestimated in more severe disease due to focus on more urgent medical concerns [24]. However, several studies have shown lower rates of anosmia in hospitalized patients compared to outpatients with COVID-19 [1,25,26].

The self-reported recovery rate of anosmia was 70 % in patients who recovered from COVID-19 symptoms, similar to other prior reports [1,37–39]. Long-term recovery at 12 months has been reported to be 96 % amongst 97 patients undergoing objective olfactory testing in one study [40], but only 54.9 % in another study [41]. One study showed only a 38.2 % full recovery rate at two years after COVID-19 diagnosis [42]. At 6 months after diagnosis, anosmia recovery was reported to be 81 % and 86 % in two separate studies [31,43]. Short-term recovery is low, with improvement only noted in 27 % of patients at a mean time of 7.2 days after COVID-19 diagnosis [9]. Altundag et al. reported that patients with isolated anosmia in the absence of other sinonasal symptoms had lower recovery rates [44]. In contrast, 9 of 10 (90 %) patients with isolated anosmia in our cohort achieved anosmia recovery. Furthermore, of 41/69 (59.4 %) patients with pre-diagnosis anosmia achieved recovery, whereas 98/151 (64.9 %) of post-diagnosis anosmia achieved recovery. Callejon-Leblic et al. and Khan et al. showed that older adults had a lower rate of recovery (OR 0.27, 95 % 0.10–0.76) [41,43]; however, there were no significant differences in age between those who recovered and those who had persistent anosmia in our study. Tipirdamaz et al. showed that asthma was significantly higher in patients with persistent olfactory dysfunction (20.5 % vs. 7.4 %, $p = 0.006$) [45]. In our cohort, there were no significant associations between medical comorbidities and development of anosmia or resolution of anosmia in our study.

Patients with persistent anosmia may have more extensive destruction of the olfactory epithelium. This may be mediated through dysautonomia, production of ACE2 antibodies, and persistent immune reaction after COVID-19 viral infection [53]. Alternatively, persistent anosmia may be due to persistent COVID-19 viral infection [48]. Some studies have found no correlation between viral load and severity of olfactory loss [54]. Although our study did not assess viral load, our findings show that the minority of patients with persistent anosmia had active COVID-19 infection and thus are expected to recover smell sensation with time, but a subset of patients who recovered from COVID-19 symptoms may have more persistent slow-resolving anosmia.

4.1. Limitations

Although the strengths of this study lie in the large sample size and laboratory-confirmed COVID-19 diagnosis, there were several limitations. The survey instrument assessed subjective self-reported OD, and thus was unable to objectively distinguish between OD states such as

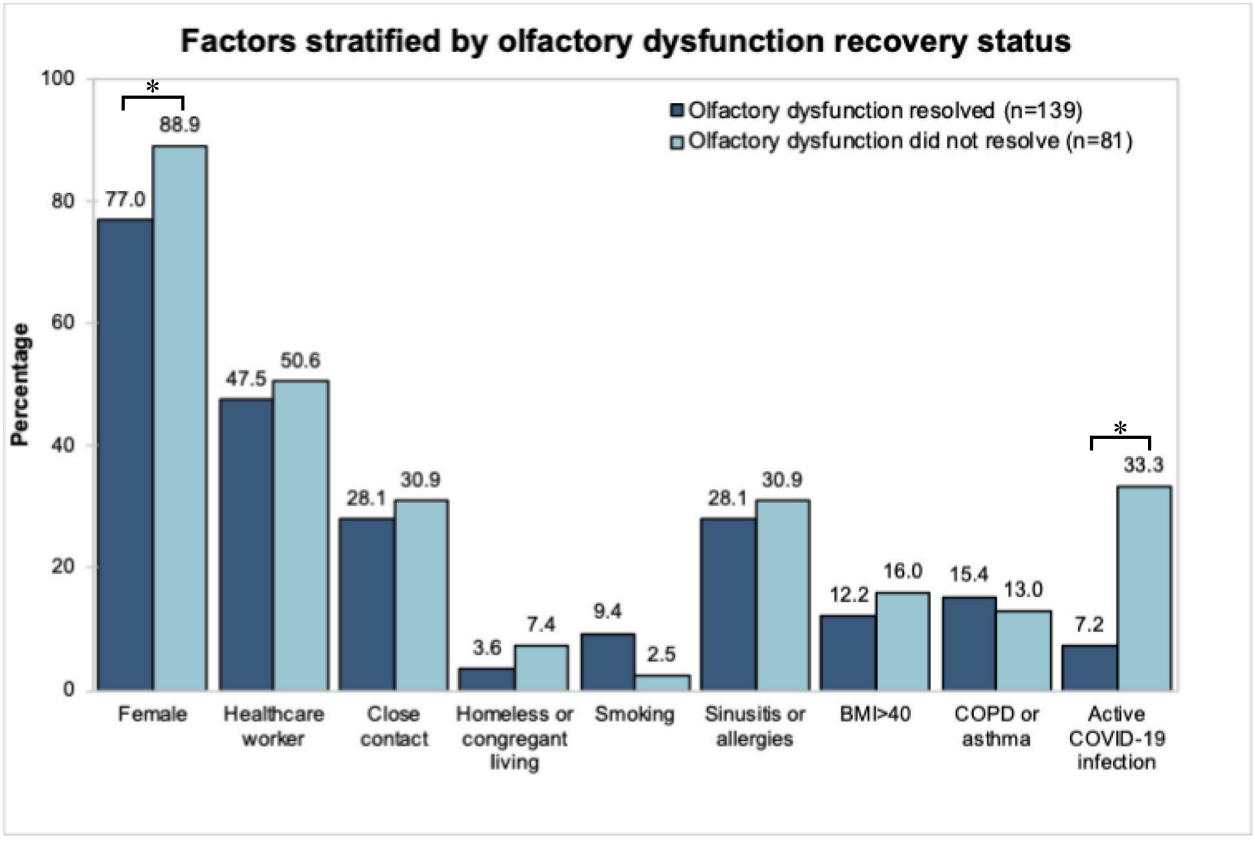

Fig. 2. Demographic, clinical, and social factors stratified by olfactory dysfunction recovery status.

hyposmia, parosmia, and anosmia. A prior study has suggested that some patients report persistent OD but do not have objective results on psychophysical evaluations [55]. In contrast, other reports show self-reported normal sense of smell but abnormal results on Smell Identification Test (UPSIT) testing [56,57]. Future studies may validate subjective smell perceptions with olfactory testing. Responses from patients with a longer time interval between COVID-19 infection and survey completion may be affected by recall bias. Response biases depending on severity and recency of OD amongst respondents, as patients with current, active, or more severe OD may be more compelled to participate in the study. As such, the reported rate of OD development may be overestimated, and rate of resolution may be underestimated. Although all patients had a positive COVID-19 test result, different strains of the SARS-CoV-2 virus throughout the course of the ongoing pandemic may have differing effects on the clinical course [58]. Survey responses for children were completed by an adult caretaker, and olfactory dysfunction in children may be difficult to validate. Half of study respondents were healthcare workers, due to the institution providing accessible to COVID-19 testing to its employees, which may limit external validity of study findings. Furthermore, this study did not evaluate treatments and their potential effects on anosmia recovery [59–65].

5. Conclusion

This prospective, observational survey study including 608 patients with COVID-19 infection revealed an olfactory dysfunction incidence rate of 36 %, and a recovery rate of 63 %. Those with OD had a hospitalization rate of 2.7 %, lower than historic hospitalization rates for allcomers of COVID-19. Demographics, socioeconomic factors, occupational factors, and medical comorbidities were not associated with either development or resolution of OD. Although gender differences were not seen in either anosmia incidence or COVID-19 recovery, female respondents were more likely to report persistent anosmia. Overall, these findings inform the risk factors for and expected course of COVID-19 associated olfactory dysfunction.

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CRediT authorship contribution statement

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Brian D'Anza: Conceptualization, Methodology, Supervision, Writing- Reviewing and Editing.

Todd Otteson: Conceptualization, Methodology, Software, Writing-Original draft preparation, Supervision, Writing- Reviewing and Editing.

Declaration of competing interest

None of the authors have significant conflicts of interest with any companies or organizations whose products or services may be discussed in this article.

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